Remarks/Arguments

I. Status and Nature of the Amendments

Claims 1-24 were previously pending. Applicants have cancelled claims 1 and 3 in favor of new claims 25 and 26, respectively. Claims 5-11, 15-24 have been withdrawn as directed to a non-elected invention. Accordingly, claims 2, 4, 12-14 and 25-26 are pending and under Examination.

Claim 25 is supported by claim 1. Claim 26 is supported by claim 3. Claims 25 and 26 are directed to a multiplexed assay method in which multiple target analytes are assayed, using analyte binding ligands that are bound to solid supports. Support for such recitations can be found throughout the specification (please see, for example, page 5, lines 18-24; page 10, line 24 – page 11, line 5). Additionally, the claims recite that steric hindrance is used only with respect to the assay of a subset (i.e., at least one, but not all) of the target analytes, and that at least one target analyte of the sample is assayed without hindrance. Support for this recitation can be found throughout the specification (please see, for example, page 16, lines 9-18). Claims 25 and 26 also differ from claims 1 and 3 in providing improved antecedent basis. Support for these amendments can be found in the superseded claims. No new matter has been introduced by any of the requested amendments.

II. The Rejections Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 12-14 have been rejected pursuant to 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse the rejection and request reconsideration.

Specifically, in rejecting claims 1 and 3, the Examiner has advised that it is unclear how the concentration of target analyte or the extent of binding is decreased by steric interference. These claims have been cancelled in favor of new claims 25 and 26.

Applicants respectfully submit that the presently claimed invention uses steric interference to reduce the rate of binding of a subset of target analytes to their corresponding binding ligands. This reduction of binding rate allows the reaction to be terminated before full equilibrium has been reached. As a consequence, the extent of reaction is related to the integrated rate of binding, which in turn depends on the binding affinity, the amount of steric hindrance (both fixed when the assay materials are produced), and the concentration of the analyte. Measurement of the extent of binding before full equilibrium has been reached thus permits a determination of analyte concentration. It is respectfully submitted that the hindrance of binding via steric interference facilitates the determination of the presence, absence, activity or concentration of the target analyte(s), and that the rejection of the claims on this basis may be properly withdrawn.

The Examiner has additionally advised that the claims are vague in light of their recitation "other target analyte(s)" and "all other binding ligands." Applicants respectfully submit that the "other target analyte(s)" and "all other binding ligands" terms of superseding claims 25 and 26 refer to binding of other analytes within the same reaction mixture but on other solid supports. Applicants' reference to other analytes is meant to illustrate that the invention modulates the binding of selected analytes to their binding ligands without modulating the binding of other analytes to their respective binding ligands. This allows combinations of measurements for analytes of diverse concentration within a single reaction mixture. Applicants have amended the claims to more clearly advance this intent, and respectfully submit that the above-stated rejection of the claims may be properly withdrawn.

In light of the above remarks and amendments, Applicants respectfully submit that the rejection of the claims pursuant to 35 U.S.C. § 112, second paragraph, may be properly withdrawn.

III. The Rejections Pursuant to 35 U.S.C. § 102(b)

Applicants respectfully submit that the present invention comprises a salient advance in the art by providing a multiplex assay format in which sterically hindered binding conditions are employed in concert with non-hindered binding conditions so as to allow the contemporaneous analysis of multiple analytes species present in the same reaction mixture. Such an advance is submitted to be significant since the proportion of reactants, particularly sample, in a reaction mixture is a compromise between the proportions optimal for each individual analyte. Proportions appropriate for a high sensitivity assay of a low concentration analyte, which typically requires a high proportion of sample, would saturate a low sensitive assay of a high concentration analyte. The present invention, by employing steric hindrance to attenuate binding of certain analytes (e.g., high concentration or high affinity analytes), allows one to extend the range of useful compromise reaction conditions thereby allowing the low sensitivity analyte assay to run with a higher proportion of sample without signal saturation.

A. Hoffman *et al.*

Claims 1-4 have been rejected pursuant to 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,912,032 (Hoffman *et al.*). Applicants respectfully traverse the rejection and request reconsideration.

Hoffman *et al.* concerns polymer-mediated methods of analysis and separation that require adjustment and control of the polymer's "critical solution temperature." Applicants respectfully submit that the reference neither discloses nor suggests a method through which the presence, absence, activity or concentration of *multiple* target analytes present in the same reaction mixture may be determined. It is additionally submitted that the reference neither discloses nor suggests the concurrent use of multiple species of polymeric supports (i.e. so as to employ a mixture of polymeric supports some of which hinder analyte binding and some of which no not mediate such hindrance).

In light of the above remarks and amendments, Applicants respectfully submit that the rejection of claims 1-4 and 12-14 pursuant to 35 U.S.C. § 102(b) in light of Hoffman *et al.* may be properly withdrawn.

B. Sato *et al.* (1986)

Claims 1-4 have been rejected pursuant to 35 U.S.C. § 102(b) as anticipated by Sato *et al.* (1986) (J. Biomed. Mater. Res. 20:853-858). Applicants respectfully traverse the rejection and request reconsideration.

Applicants respectfully submit that Sato *et al.* (1986) concerns the use of porous alkylamine glass beads to immobilize anti-IgE antibody in order to form a carrier capable of adsorbing IgE. It is submitted that the reference neither discloses nor suggests a method relevant to the determination of the presence, absence, activity or concentration of *multiple* target analytes present in the same reaction mixture. It is additionally submitted that the reference neither discloses nor suggests the concurrent use of multiple species of particles (i.e. porous alkylamine glass particles which hinder the ability of IgE to bind to the immobilized anti-IgE antibody and porous alkylamine glass particles which do not hinder such binding).

In light of the above remarks and amendments, Applicants respectfully submit that the rejection of claims 1-4 and 12-14 pursuant to 35 U.S.C. § 102(b) in light of Sato *et al.* (1986) may be properly withdrawn.

IV. The Rejections Pursuant to 35 U.S.C. § 103(a)

A. Sato *et al.* (1986) and McHugh (1994)

Claims 12-14 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious in light of Sato *et al.* (1986) in combination with McHugh (1994) ("Flow Microsphere Immunoassay for the Quantitative and Simultaneous Detection of Multiple Soluble Analytes, "Methods in Cell Biology 42, Part B (Academic Press). Applicants respectfully traverse the rejection and request reconsideration.

As indicated above, Sato *et al.* (1986) relates to the use of porous alkylamine glass beads to immobilize anti-IgE antibody in order to form a carrier capable of adsorbing IgE. McHugh (1994) concerns a flow microsphere immunoassay for the simultaneous detection of multiple analytes, and thus relates to a bead-based multiplexed assay.

Applicants respectfully submit that the combined teachings of Sato *et al.* (1986) and McHugh (1994) fail to disclose the concurrent use of: (1) a support in which binding is sterically hindered, in concert with (2) a support having unhindered binding capabilities in order to provide a single multiplexed assay of multiple target analytes. In this regard, Sato *et al.* teaches the use of porous glass beads, and fails to teach assays that employ mixtures of different supports. It is submitted that McHugh *et al.* (1994) does not employ hindered binding supports. Thus, were its teachings altered to include Sato *et al.*-style supports, the combination would relate only to the use of a single particle type in a flow, multiplexed assay.

Significantly, by providing hindered binding and non-hindered binding supports, the presently claimed invention provides a method for accomplishing the simultaneous assaying of both high concentration and low concentration analytes. Neither Sato *et al.* (1986) nor McHugh (1994) provide teachings relevant to this goal, and thus do not suggest the multiplexed assay being claimed in which a subset, but not all, of the solid supports feature analyte binding hindered by steric interference.

Accordingly, Applicants respectfully submit that the rejection of claims 12-14 pursuant to 35 U.S.C. § 103(a) as obvious in light of Sato *et al.* (1986) in combination with McHugh (1994) may be properly withdrawn.

B. Hoffman *et al.* and McHugh (1994)

Claims 12-14 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious in light of Hoffman *et al.* in combination with McHugh (1994). Applicants respectfully traverse the rejection and request reconsideration.

As indicated above, Hoffman *et al.* concerns polymer-mediated methods of analysis and separation that require adjustment and control of the polymer's "critical solution temperature." McHugh (1994) concerns a flow microsphere immunoassay for the simultaneous detection of multiple analytes, and thus relates to a bead-based multiplexed assay.

Applicants respectfully submit that the combined teachings of Hoffman *et al.* and McHugh (1994) fail to disclose a multiplexed assay which concurrently uses supports in which binding is sterically hindered, *and* supports having unhindered binding capabilities. In this regard, neither Hoffman *et al.* nor McHugh (1994) employ hindered binding supports. Thus, the combined teachings of these references would relate only to the use of a Hoffman *et al.* particle type in the flow, multiplexed assay of McHugh (1994).

As discussed, above, by providing hindered binding and non-hindered binding supports, the presently claimed invention provides a method for accomplishing the simultaneous assaying of both high concentration and low concentration analytes. Neither Hoffman *et al.* nor McHugh (1994) provide teachings relevant to this goal, and thus cannot be deemed to suggest the multiplexed assay being claimed.

Accordingly, Applicants respectfully submit that the rejection of claims 12-14 pursuant to 35 U.S.C. § 103(a) as obvious in light of Hoffman *et al.* in combination with McHugh (1994) may be properly withdrawn.

V. Concluding Remarks

Applicants submit that the present response is complete and complies with the requirements of 35 U.S.C. §121. The Application is believed to be in condition for Allowance and early notice of such favorable action is respectfully requested. Should the Examiner have any remaining questions regarding the subject invention or its patentability, Applicants encourage the Examiner to contact the undersigned to answer such questions or provide any desired additional information.

Respectfully Submitted,

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Edell, Shapiro & Finnan, LLC
1901 Research Blvd., Suite 400
Rockville, MD 20850
Telephone: (301) 424-3640
Facsimile: (301) 762-4056

/Jeffrey I. Auerbach/
Jeffrey I. Auerbach
Registration No. 32,680
Attorney for Assignee

Customer No. **52287**